REMARKS/ARGUMENTS

The Pending Claims

Claims 1-28 were pending. Claims 4-6, 8-10, 14, 15, 17-26, and 28 stand withdrawn as drawn to a non-elected invention. Claim 1 is currently amended, as are withdrawn claims 4-6, 14, 17, and 20-22. Claims 3 and 19 are cancelled herein.

Amendments to the Claims

Claim 1 is amended to recite the terms of original claim 3. Likewise, withdrawn claims 14 and 17 are amended to recite similar terms. Withdrawn claims 4-6 and 20-22 are amended to independent form. Minor formatting amendments are also made to these claims.

Claims 1, 14, and 17 are further amended to insert the term "wherein the poly(ethylene) glycol residue is covalently linked to said amino acid residue of said peptide via an intact glycosyl linking group," and to otherwise correct typographical errors and to improve the grammar of the claims. Support for the amendments can be found throughout the specification, notably at paragraph 0101 of the specification.

No new matter is added by these amendments.

Priority

The Interview Summary dated August 19, 2010 states that the pending claims are accorded a priority date of December 3, 2004, i.e., the filing date of International Patent Application PCT/US204/041004. Applicants respectfully submit that the structures of the pending claims are entitled to a priority date of at least September 29, 2004, which is the filing date of U.S. Provisional Patent Application 60/614,518 (see, e.g., paragraph 0109 et seq.). Support for such PEG structures is further provided in text form at paragraph 0117 of U.S. Provisional Patent Application 60/592,744, filed July 29, 2004. Exemplary support for the PEG-modified sialic acid moiety, to which these PEG structures are applied, can be found in a yet earlier application, U.S. Provisional Patent Application 60/526,796, filed December 3, 2003, at page 24, lines 1-7. Applicants therefore request reconsideration of the priority of the pending claims.

Discussion of Information Disclosure Statement

The Office Action indicates that Copeland, Takeda, and Wang, cited in the Information Disclosure Statement filed December 4, 2008, were not considered as one or more pages of each reference were missing or illegible. Replacement copies of these references are submitted herewith. The Examiner indicates that the "article from Endocrine, vol. 11, p. 205-215" was not considered because a copy of the article was not provided and the year of publication for the article was not provided. Applicants respectfully note that the term "Endocrine, vol. 11, p. 205-215" was simply a continuation of the citation begun on the last line of the preceding page, namely "Ulloa-Aguirre et al., 1999, Role of Glycosylation in Function of Follicle-Stimulating Hormone, Endocrine, vol. 11, p. 205-215," which reference has not been objected to. Therefore, Applicants do not provide a replacement copy of this reference which was previously submitted and already has been considered by the Examiner.

The Office Action indicates that non-patent literature documents HW (Harris) and HX (Harris et al.) identified in the Information Disclosure Statement dated June 3, 2010, were not considered by the Examiner. A similar objection has been made to the Hermanson references cited in the Information Disclosure Statement filed December 4, 2008. The Information Disclosure Statement submitted herewith contains corrected citations for these non-patent literature documents, in which the corrected citations contain an indication that only the title pages are provided for the Harris references, and only the tables of contents are provided for the Hermanson references.

Discussion of Rejection Under 35 U.S.C. § 102

Claims 1, 2, 7-13, 16, and 27 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 02/031464 to DeFrees as evidenced by Oh-eda et al., *J. Biol. Chem.*, 265: 11432-11435 (1990). In the interest of advancing prosecution, independent claim 1 has been amended to include the terms of claim 3, which is not indicated to be anticipated by the cited references. Therefore, Applicants respectfully submit that this rejection has been rendered moot and should be withdrawn.

Discussion of Rejection Under 35 U.S.C. § 103(a)

1. Section 0001

Claim 3 is rejected as allegedly obvious over WO 02/031464 to DeFrees as evidenced by Oh-eda et al., *J. Biol. Chem.*, 265: 11432-11435 (1990), and further in view of U.S. Patent 5,643,575 (Martinez et al.), WO 99/55376 (El-Tayar et al.), and Felix et al., *J. Peptide Res.*, 63: 85-90 (2004).

The Office Action alleges that DeFrees teaches a glycopegylated G-CSF as well as methods for producing such structures. However, the Office Action admits that DeFrees does not teach or suggest the specific branched PEG structures of claim 3 (Office Action, page 11). Oh-Eda is cited as allegedly providing the native O-glycosylation structure of hG-CSF, but is also not alleged to teach or suggest any pegylated structures.

In alleging the structures of claim 3 to be obvious, the Office Action cites Martinez, Felix, and El-Tayar as providing evidence that branched PEG structures having amino acid cores were known in the art and that the claimed structures could have been prepared using the teachings of the cited references. The Office Action cites Martinez as allegedly teaching the "conjugation of branched, non-antigenic PEG polymers to biologically active molecules ... e.g., G-CSF, as a means to extend their circulating half life" (Office Action, page 14). The Office Action further alleges that Martinez teaches that "branched PEG polymers can be synthesized by using any linker that comprises a multiply-functionalized alkyl group," including lysine (Office Action, page 15). The Office Action alleges that Felix likewise teaches "a branched bis-pegylating reagent wherein lysine is used as the linker, and a tris-pegylating reagent wherein glutamate-lysine is used as the linker" (Office Action, page 13). In considering these references, the Office Action concludes that "one of ordinary skill in the art would have been motivated to substitute the lysine linker backbone as disclosed in the Martinez '575 patent with other amino acids, such as serine or cysteine" (Office Action, page 15).

Applicants respectfully submit that neither Martinez nor Felix teaches a method by which the presently claimed structures could be prepared. Martinez allegedly provides a "branched PEG structure wherein lysine is the linker conjugated to two linear mPEG

compounds (Office Action, page 13). The cited portion of Martinez (col. 13, lines 20-40) allegedly produces a branched polymer having a lysine core by reacting a p-nitrophenyl PEG (PNP-PEG) with lysine ethyl ester. Preparation of U-PNP-PEG is described at Examples 1-2 (col. 9, line 54 – col. 10, line 40) of Martinez, which rely on the reaction of 1, 3-diamino-2-propanol with mPEG-N-succinimidyl carbonate (SC-PEG). The reagents and conditions provided in Martinez, therefore, apply only to linkage of an amide group. Martinez provides no teaching or suggestion of how to prepare branched PEG structures using an ether or thioether as provided in the pending claims. Moreover, Martinez fails to teach any reaction conditions wherein the two PEG groups are not attached to the core using identical amide linkage. Therefore, Martinez does not apply to the asymmetrical structures of the pending claims which include both amide and ether or thioether linkages.

Felix likewise fails to teach the structures of the pending claims, or a method by which such structures could be produced. Although the Office Action alleges that Figure 2 of Felix teaches "methods for the preparation of the bis-pegylating reagent and tris-pegylating reagent" (Office Action, page 13), Applicants respectfully submit that the methods of Felix employ strategies for synthesis that result in a structurally distinct branched PEG from those of the pending claims. As shown in Figure 2 of Felix, the lysine core is linked to the peptide (glutamate) via the N-terminus of the lysine. One of the two PEGs of Felix is attached to the amide group of the lysine side chain, while the other PEG is attached to the C-terminus of the lysine. In contrast, in the structures of the pending claims, the carboxy terminus of the amino acid core is conjugated to the sialic acid moiety, while the two PEGs are attached to the side chain and the N-terminus of the amino acid. Structural differences result from these differing linkages. First, the linkage of a PEG as provided in Felix at an N-terminus of an amino acid as in the pending claims cannot result in the peptide-type linkage prepared in Step 1 of Figure 2 of Felix (i.e., Fmoc-Lys(Boc)-NH-CH_2-O-PEG_A). Second, the linkage of PEG to the lysine side chain as taught by Steps 3a-3b of Figure 2 of Felix (wherein COOSu-CH_2-O-PEG_B is applied to a TFA-deprotected amide group) cannot merely be replaced by linkage to a serine or cysteine side chain to yield the presently claimed structures. A carboxy group, rather than the simple ether or thioether of the pending claims, would result. In the absence of reagents and reaction conditions for employing amino acids other than lysine, Felix cannot be extended to teach the use of serine or cysteine as a PEG linker, and moreover, even if serine

or cysteine were employed in the steps of Felix, the branched PEG structures of the pending claims would not result.

El-Tayar, also fails to cure any of the defects of Martinez or Felix. The Office Action cites El-Tayar as allegedly teaching "the use of amino acids, such as serine, as bifunctional linkers." (Office Action, page 15). However, the portion of El-Tayar referenced by the Office Action indicates only that the serine residue of a luteinizing hormone releasing hormone (LHRH) analog can be pegylated, and that the serine residue can be linked to the PEG by an amino acid (such as glycine). El-Tayar does not teach or suggest the use of serine (or any amino acid) to prepare any branched PEG. Therefore, El-Tayar does not cure any defect of Martinez or Felix.

Because Felix, Martinez, and El-Tayar fail to cure the defects of DeFrees (and Oh-Eda), namely the absence of the branched PEGs of the pending claims, the cited combination of references fails to teach each and every element of the pending claims. Therefore, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

2. Section 0002

Claim 3 is further rejected as allegedly obvious over EP 0605963 (Wright) as evidenced by U.S. Patent 6,586,398 (Kinstler), in view of U.S. Patent 5,824,778 (Ishikawa), U.S. Patent Application Publication 2002/0016003 (Saxon), U.S. Patent 5,643,575 (Martinez et al.), and Monaco et al., *Gene* 180: 145-150 (1996), as evidenced by Nagata et al., *EMBO J.*, 5(3): 575-581 (1986), and Oh-eda et al., *J. Biol. Chem.*, 265: 11432-11435 (1990).

The pending claims are directed to a G-CSF peptide covalently linked to a branched poly(ethylene glycol) residue having particular serine or lysine-based structures, via an intact glycosyl linking group.

Wright, Kinstler, Ishikawa, Martinez, Monaco, Nagata, and Oh-eda do not teach or suggest a G-CSF peptide coupled to a modifying group via an "intact glycosyl linking group" as recited in the pending claims. In particular, the Office characterizes Wright as teaching "methods for the modification of a peptide ... wherein EPO is oxidized with sodium periodate followed by conjugation of the resulting aldehyde to PEG" (Office Action, page 17-18). Likewise, while the Office cites Kinstler as teaching PEGylation of NESP, the Office

specifically indicates that Kinstler teaches use of "10mM sodium periodate oxidation of EPO targets the pendant diol of the penultimate glycosyl unit sialic acid residue" (Office Action, page 18). The present application explicitly indicates at, for example, specification paragraph 0049, that an "intact glycosyl linking group" is not oxidized by sodium periodate. Therefore, neither Wright nor Kinstler teaches an "intact glycosyl linking group" as recited in the pending claims and as defined by the present specification. Likewise, Ishikawa, Monaco, Nagata, and Oh-eda are not cited as teaching an "intact glycosyl linking group," and indeed these references do not teach an "intact glycosyl linking group."

The remaining cited reference, Saxon, also fails to teach or suggest a G-CSF peptide coupled to a modifying group via an "intact glycosyl linking group" as recited in the pending claims. Indeed, the methods disclosed in Saxon cannot be extended to, for example, couple PEG to a peptide via an "intact glycosyl linking group" as recited in the pending claims.

The cell surface ketone reactions described and shown at paragraphs 0008 through 0010 of Saxon, which Saxon identifies as prior art, involve the application of N-levulinoylmannosamine ("ManLev") to living cells, which "permits the metabolism of the unnatural ManLev precursor into sialic acid analogs on living cells, resulting in the display of ketones ... on the cell surface" (Saxon, paragraph 0008). Saxon alleges that these displayed ketones can then be further modified "with any moiety bearing a hydrazide or aminooxy group" (Saxon, paragraph 0008). However, such a statement appears to overreach the actual disclosure of the reference cited, namely Mahal et al., *Science*, *276*: 125 (1997). In particular, Mahal recites only the linkage of biotinamido-caproyl hydrozide, which is a small biotin-based molecule (Mahal, page 1126). Although Mahal speculates that "[i]n principle, any hydrazide-derivatized molecule can be used to selectively remodel the surface of ketone-expressing cells" (Mahal, page 1126, Figure 1 legend), Saxon's own disclosure demonstrates that an azide coupling is not equally successful for all reagents. One of ordinary skill in the art would not have reasonably believed, based on Mahal's and Saxon's disclosures, that PEG could be successfully conjugated using the reactions and reagents provided therein.

Some limitations of this type of azide coupling are shown at Figure 13 of Saxon, which is described in Example 7, wherein an acetate-amide linkage is unsuccessfully attempted. Saxon notes that while both anhydrous and aqueous conditions were studied,

"only azide reduction to the amine was observed, without the desired acetate transfer." (Saxon, paragraph 0211). Saxon posits that the reaction might be successful if one were to "increase the rigidity of the linkage between the phospine and the ester, as in ... Scheme 18, for the desired reaction to take place" (Saxon, paragraph 0211). The reaction depicted in Scheme 18, however, appears to be merely prophetic with no evidence that it would be more successful than the failed reaction of Figure 13 (and neither Scheme 18 nor Figure 13 depicts a linkage that would conform precisely to C_5 or C_9 of pending claim 215). In fact, nearly all of the reactions which were allegedly successfully completed by Saxon include an aromatic linker. See, e.g., Example 6 and Example 8 of Saxon, with accompanying figures. The other ligation reaction recited by Saxon, a peptide-peptide linkage provided in Example 7, also represents a particular situation in which the connected moieties are designed for stability, and further includes aryl or cycloalkyl groups. Specifically, R_1 and R_2 as required in Scheme 14 are defined at paragraphs 0080 and 0081 of Saxon. R_1 is defined as "an electrophilic group to trap (e.g., stabilize) an aza-ylide group," while R_2 is defined as follows: "R_2 and R_3 are generally aryl groups, including substituted aryl groups, or cycloalkyl groups (e.g., cyclohexyl groups) where R_2 and R_3 may be the same or different, preferably the same."

Because Saxon relies upon the importance of a "rigid linkage" such as an aryl or additional cycloalkyl, in combination with an electrophilic "trap," to support the moieties being attached, one of ordinary skill in the art would not have reasonably expected a relatively fluid molecule such as PEG to be suitable for conjugation using the methods disclosed therein. Similar to the Office Action's characterization of the deficiency of Wright, Saxon fails to "expressly teach conjugation of the PEG polymer to the 9-position or 5-position of sialic acid, as recited in the instant claims." Therefore, Saxon does not cure the deficiency of the other cited references which fail to recite a G-CSF peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed.

The Office alleges that it would have been obvious to combine the teachings of Wright and Kinstler regarding methods of conjugation of PEG to the proteins disclosed therein with the methods of Ishikawa regarding G-CSF, with the methods of Saxon regarding conjugation of hydrazine or phosphine groups, with the methods of Martinez regarding the structure of the branched PEGs, and further with the disclosures of Nagata, Oh-eda, and Monaco regarding the structure and expression of G-CSF (Office Action, page 21).

However, inasmuch as none of the cited references provide a G-CSF peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed, the combination of all of these references does not provide a G-CSF peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed, such that the presently claimed invention must be considered unobvious over the combination of the cited references. Furthermore, none of the cited references provide branched PEGs as presently claimed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

3. Section 0003

Claim 3 is further rejected as allegedly obvious over EP 0605963 (Wright) as evidenced by U.S. Patent 6,586,398 (Kinstler), in view of U.S. Patent 5,824,778 (Ishikawa), U.S. Patent Application Publication 2002/0016003 (Saxon), in view of U.S. Patent 5,643,575 (Martinez et al.), in view of Monaco et al., *Gene* 180: 145-150 (1996), as evidenced by Nagata et al., *EMBO J.*, 5(3): 575-581 (1986), and Oh-eda et al., *J. Biol. Chem.*, 265: 11432-11435 (1990), in view of WO 99/55376 (El-Tayar et al.), and in view of Felix et al., *J. Peptide Res.*, 63: 85-90 (2004) .

The Office Action references section 0002 with respect to the teachings of Wright, Kinstler, Ishikawa, Saxon, Monaco, Martinez, Nagata, and Oh-eda. The Office Action references section 0001 with respect to the teachings of Felix and El-Tayar.

As described above, Applicants respectfully submit that the cited references, alone or in any combination, do not teach or suggest the particular branched polymer structures as presently claimed, nor do they teach a G-CSF peptide coupled to PEG via an "intact glycosyl linking group" as presently claimed. The deficiencies of these references vis-à-vis the presently claimed invention are discussed in sections 0001 and 0002 and are not eliminated by any combination of these references. The presently claimed invention, therefore, must be considered unobvious over the combination of these references. Accordingly, Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Obviousness-Type Double Patenting

Claims 1, 2, 7, 8, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patent 7,138,371.

Claims 1, 2, 7-9, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patents 7,173,003 and 7,416,858.

Claims 1, 2, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patents 7,473,680 and 7,691,603.

Claims 1, 2, 10, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patent Application 10/585,385.

Claims 1, 2, 11, 13, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patent Application 11/794,560.

Claims 1, 2, and 16 are rejected for alleged obviousness-type double patenting over U.S. Patent Application 11/867,553

Claims 1, 2, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patent Applications 11/597,258, 11/866,969, 12/152,587, 12/418,530, 12/443,428, 12/496,595, and 12/663,056.

Claims 1-3, 7, 8, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patent Application 11/166,404.

Claims 1-3, 7-13, 16, and 27 are rejected for alleged obviousness-type double patenting over U.S. Patent Application 11/652,467.

Applicants note that claim 3 had not been rejected for obviousness-type double patenting over U.S. Patent 7,138,371, 7,173,003, 7,416,858, 7,473,680, or 7,691,603, or U.S. Patent Application 11/794,560, 12/152,587, 10/585,385, 11/597,258, 11/866,969, 12/418,530, 12/443,428, 12/496,595, 12/663,056, or 11/867,553. Claim 1 has been amended to recite the terms of claim 3. Accordingly, Applicants respectfully submit that the double patenting rejections over the foregoing patents and patent applications have been rendered moot and should be withdrawn.

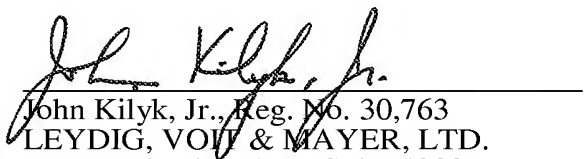
With respect to U.S. Patent Applications 11/652,467 and 11/166,404, since these obviousness-type double patenting rejections are provisional, Applicants respectfully request

these obviousness-type double patenting rejections be held in abeyance until one or more claims of the present application are otherwise deemed allowable.

Conclusion

Applicants respectfully submit that the patent application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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